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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/696,872 | 10/26/2000 | James E. Rothman | 11746/46603 | 1809 |

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EXAMINER

SWOPE, SHERIDAN

| ART UNIT | PAPER NUMBER |
|----------|--------------|
| 1652 | 160 |

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/696,872 | ROTHMAN, JAMES E. | |
| | Examiner | Art Unit | |
| | Sheridan L. Swope | 1652 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 06 July 2003.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 20-26,28-37 and 44-73 is/are pending in the application.
- 4a) Of the above claim(s) 20-26,28,33-37,44-48,50-56,58,59,61 and 64-72 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 29-32,57,60,62,63 and 73 is/are rejected.
- 7) Claim(s) 29, 31,49,60,62, 63 and 73 is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10,15.
- 4) Interview Summary (PTO-413) Paper No(s). _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

DETAILED ACTION

Applicant's election, without traverse of Invention II, Claims 29, in part, 30-35, 37, 45, 47, 49, 57, 59-71, 73, and 75 in Paper No. 14 is acknowledged. Applicant's election, without traverse of the species pentamerization domains, the KDELr inhibitor set forth by SEQ ID NO: 23 or encoded by SEQ ID NO: 24, the method of expressing the KDEL receptor in a cell by introduction of a nucleic acid, folate as the conjugated moiety, melanoma, and Lys as the X in X-Asp-Glu-Leu is acknowledged. In a telephone conversation with Joseph Coppola on September 18, 2003, the election of Lys, as the X in XDEL, for both the hsp and the KDEL receptor inhibitor was confirmed. Applicant's amendment of Claims 34 and 37 is acknowledged. Claims 20-26, 28, 33-37, 44-48, 50-56, 58, 59, 61, and 64-72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claims 29, in part, 30-32, 49, 57, 60, 62, 63, and 73 are hereby considered.

Information Disclosure Statement

Since neither the Applicants nor the Office can locate either the Information Disclosure Statement or the 1449 form for the Information Disclosure Statement submitted July 3, 2002, the references therein have not been considered.

Claims-Objections

Claims 29, 49, 60, 62, 63, and 73 are objected to for reciting subject matter drawn to nonelected Inventions.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-32, 57, 60, 62, 63, and 73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For said Claims the “X” in XDEL has not been identified as a Lys residue, and yet, Applicants have elected Lys as the residue in the “X” position. For these reasons, Claims 29-32, 57, 60, 63, and 73 are confusing.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of Claims 29-32 under 35 U.S.C. 112, first paragraph is maintained. New Claims 49, 57, 60, 62, and 63 are rejected under 35 U.S.C. 112, first paragraph for the same reasons described for Claims 20-37 in the prior action.

Applicants have argued that the specification is enabling of the recited invention. Applicants state that, “The Examiner’s argument is based on the erroneous assumption that changing the amino acid sequence of the claimed proteins anywhere (e.g., outside of the regions of the oligomerization domain and the X-Asp-Glu-Leu sequence) would affect the function of the proteins. This assumption is erroneous because the recited oligomerization domains and X-Asp-Glu-Leu sequences are modular. They are amino acid sequences which are able to carry out their function irrespective of the larger context into which they are placed.”

In view of these arguments, the Examiner makes the following comments. The presently recited invention, in which both the hsp and the KDEL receptor inhibitor have Lys as the X in

the XDEL motif, is enabled by the specification and the prior art (see the 35 USC 103 rejection below). However, it has not been proven that any protein comprising XDEL at the C-terminus, wherein X is any amino acid, will be retained in the endoplasmic reticulum (ER). In fact, Wilson et al, 1993 teach that lysozyme-SEHDEL is retained in the ER, while lysozyme-FEHDEL is not (Fig 3). Furthermore, the peptide LNYFDDEL is two-orders of magnitude less effected than the peptide YTFEHDEL in blocking the binding of the peptide [¹²⁵I]-YTSEKDEL to the KDEL receptor (Fig 1). These data argue that (i) not all XDEL motifs are sufficient for binding to the KDEL receptor and (ii) the sequence upstream of a XDEL motif can affect the ability of a protein to bind to the KDEL receptor. A lower binding affinity of an “inhibitor” peptide compared to the hsp would likely result in little or no ability to “inhibit” binding of the hsp or promote of secretion of the bound antigenic peptide. For these reasons, rejection of Claims 29-32 under 35 U.S.C. 112, first paragraph is maintained and new Claims 49, 57, 60, and 63 are rejected under 35 U.S.C. 112, first paragraph for the same reasons described in the prior action.

Rejection of Claims 29-32 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is also maintained. New Claims 49, 57, 60, 62, and 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons described for Claims 20-37 in the prior action.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 29, 31, 57, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Munro et al, 1987 in view of Wilson et al, 1993 and further in view of Multhoff et al, 1998 and Bandman, 1998. Munro et al teach that deletion of the C-terminal KDEL sequence from the hsp BiP results in secretion of the variant BiP upon expression in COS cells (Fig 3). Munro et al do not teach induction of hsp secretion using a KDEL receptor inhibitor comprising the C-terminal sequence KDEL. Wilson et al teach that peptides comprising the KDEL sequence inhibit binding of the peptide [¹²⁵I]-YTSEKDEL, which corresponds to the 7 C-terminal residues of BiP (Fig 1). Neither Munro et al nor Wilson et al teach that hsp proteins complex with antigenic peptides; however, said teachings were known in the art. For example, Multhoff et al teach that hsps possess the capacity to bind peptides, that this chaperoning function indicates a role in antigen processing and presentation (pg 87, parg 2), and that hsps elicit an immune response if they are on the plasma membrane (pg 86, parg 5). It would have been obvious to a person of ordinary skill in the art to use the method of Wilson et al, to use peptides containing the KDEL motif to induce secretion of a hsp/antigenic peptide complex from the cell. The use of the methods of Wilson et al, to use KDEL receptor inhibitors to induce secretion of a hsp/antigenic peptide complex from the cell is suggested by Bandman et al wherein they teach inhibitors of KDEL receptors as therapeutic agents to treat diseases involving retention of proteins in the ER (col 17, lines 6-8). Motivation to use the method of Wilson et al, to use peptides containing the

KDEL motif to induce secretion of a hsp/antigenic peptide complex from the cell is provided by the desire to increase the immune response by increasing the translocation of the hsp/antigenic peptide complex from the ER to the cell surface. The expectation of success is high, as the KDEL receptor inhibitor peptides have been used successfully to block binding of hsps to the KDEL receptor and deletion of the C-terminal KDEL motif from hsps results in secretion. Therefore, Claims 29, 31, 57, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Munro et al, 1987 in view of Wilson et al, 1993 and further in view of Multhoff et al, 1998 and Bandman, 1998.

Applicants' statements filed March 12, 2003 as Paper No. 11 (pg 15, parg 3-pg 16, parg 6), support this rejection of Claims 29, 31, 57, and 73 under 35 U.S.C. 103(a). Applicants state that, "the recited ...X-Asp-Glu-Leu sequences are modular. They are amino acid sequences, which are able to carry out their function irrespective of the larger context into which they are placed. In other words, they are sufficient to independently confer upon the protein in which they are found the characteristics of ...KDEL receptor binding". In support of said statement, applicants cite Wilson et al, Kim et al, 1998, Townsley et al, 1993, and Lewis et al, 1992. It is acknowledged that the prior art provide evidence, as described above, that the KDEL motif at the C-terminus of a protein is sufficient to cause retention of the protein in the ER.

Claims 30 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Munro et al, 1987 in view of Wilson et al, 1993, Multhoff et al, 1998, and Bandman, 1998 and further in view of Wearsch et al, 1996 and Hoogewerf et al, 1997. The teaching of Munro et al Wilson et al, Multhoff et al, and Bandman are described above. The combination of Munro et al Wilson et al, Multhoff et al, and Bandman do not teach a KDEL receptor inhibitor comprising an

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oligomerization or pentamerization domain. Wearch et al teach that the gp94 hsp, which has a KDEL motif, has an oligomerization domain at residues 676-719 (Abstract). Since hsp containing KDEL receptor binding motifs can be oligomeric, it would have been obvious to a person of ordinary skill in the art to make KDEL receptor inhibitors that are oligomeric. Furthermore, as stated by the Applicants, one skilled in the art would find it routine to choose a suitable oligomerization domain for use in the claimed methods (Paper No. 11; pg 19, parg 2, lines 1-2). To make KDEL receptor inhibitors that are oligomeric is suggested by Wearch et al, wherein they teach that oligomerization of a ligand produces a higher effective concentration of the ligand at the receptor (pg 13577, parg 3). Thus, motivation is provided by the desire to make a KDEL receptor inhibitor that more effectively blocks binding of the hsp/antigenic complex to the KDEL receptor. The expectation of success is high, as recombinant oligomeric proteins are known in the art. Therefore, Claims 30 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Munro et al, 1987 in view of Wilson et al, 1993, Multhoff et al, 1998, and Bandman, 1998 and further in view of Wearsch et al, 1996 and Hoogewerf et al, 1998, as well as admission by the Applicants.

Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Munro et al, 1987 in view of Wilson et al, 1993, Multhoff et al, 1998, and Bandman, 1998 and further in view of Leamon et al, 1991. The teaching of Munro et al Wilson et al, Multhoff et al, and Bandman are described above. The combination of Munro et al Wilson et al, Multhoff et al, and Bandman do not teach a KDEL receptor inhibitor conjugated to folate. However, internalization of protein/folate conjugates was known in the art. Leamon et al teach that macromolecules can be delivered into living cells by folate receptor-mediated endocytosis of the macromolecule

conjugated to folate (Fig 1). It would be obvious to a person of ordinary skill in the art to use a KDEL receptor inhibitor conjugated to folate in the method of Claim 29. To do so is suggested by Leamon et al, wherein they state that folate conjugates are internalized in a nondestructive manner and that said conjugates remain active. The ability of such a conjugate to be internalized and be effective intracellularly would motivate one to do so. The expectation of success is high, as many different kinds of macromolecules conjugated to folate can be delivered into living cells (Leamon et al). Therefore, Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bandman et al, in view of Wilson et al, Multhoff et al, and Mazzarella et al, and further in view of Leamon et al, 1991.

Claim 63 is rejected under 35 U.S.C. 103(a) as being unpatentable over Munro et al, 1987 in view of Wilson et al, 1993, Multhoff et al, 1998, and Bandman, 1998 and further in view of Tamura et al, 1997. The teaching of Munro et al Wilson et al, Multhoff et al, and Bandman are described above. The combination of Munro et al Wilson et al, Multhoff et al, and Bandman do not teach methods of inducing secretion of a hsp/antigenic peptide complex from a cell using a KDEL receptor inhibitor wherein the antigenic peptide is derived from a melanoma. Tamura et al teach that treatment with a GP96hsp/melanoma-derived peptide complex reduces the growth rate of a melanoma tumor (Fig 3A; pg119, parg 2). It would be obvious to a person of ordinary skill in the art that treatment with a KDEL receptor inhibitor would increase cellular secretion of the GP96/melanoma-derived peptide complex, since said hsp comprises a KDEL motif. To do so is suggested by Tamura et al, wherein they state that increasing the concentration of an hsp/tumor-derived antigenic peptide complex is an effective immunotherapy of cancers (Abstract). Motivation to use a KDEL receptor inhibitor to induce cellular secretion of an

hsp/melanoma-derived peptide complex derives from the ability of the immune system to generate antibodies to the melanoma-derived peptide and, thus, fight the melanoma. The expectation of success is high, as KDEL receptor inhibitor peptides have been used successfully to block binding of hsps to the KDEL receptor and deletion of the C-terminal KDEL motif from hsps results in secretion (see above). Therefore, Claim 63 is rejected under 35 U.S.C. 103(a) as being unpatentable over Munro et al, 1987 in view of Wilson et al, 1993, Multhoff et al, 1998, and Bandman, 1998 and further in view of Tamura et al, 1997.

Allowable Subject Matter

Claim 49 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.
Sheridan L. Swope, Ph.D.

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